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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,012	SANDBERG ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,4,5,7-10,18,21,26-28,30-32 and 46-58* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 4-5, 7-10, 18, 21, 26-28, 30-32 and 46-58* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 4-5, 7-10, 18, 21, 26-28, 30-32 and 46-58 are pending and being acted upon in this Office Action.

2. Applicant's request for interview is acknowledged. A telephone call was made to Suzannah K Sundby on Monday September 26, 2011, but did not reach Applicant's representative. It is suggested that Applicant call the Examiner of record to reschedule the interview after receiving this Office Action.

Specification

The disclosure stands objected to because the use of the trademark MITRATAG 1033, Herceptin, MitraDept should be capitalized *wherever* it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The disclosure is further objected to because of the following informalities: (A) "radio nuclide" at page 11, line 8, page 16, line 4 should be one word "radionuclide". (B) The phrase "claims 33-45" at page 17, line 29 is objected to because said claims 33-45 have been canceled. (C) The punctuation marks in the phrase "Fab'. F(ab')2." should have been ",". (D) The phrase "anti Erb" should have been "anti-Erb" at page 25, line 3 and page 30, line 25. (E) Typographical error "F(ab'') should have been "F(ab')". Correction is required in response to this Office Action.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The request this objection be held in abeyance until an indication of allowable subject matter is acknowledged.

Objection and Rejection Withdrawn

The objection to claims 1-2, 4, 5, 30, 46, 51 and 57 has been obviated by the claims amendment filed June 29, 2011.

The rejection of claims 8, 13, 18, 21 26-28, 30, 31, 46, 48, 49, 50, 52, 54, 56 and 58 under 35 U.S.C. 112, second paragraph has been obviated by the claims amendment filed June 29, 2011.

The written description and enablement rejections of claims 1-2, 4-5, 7-10, 12-14, 18, 21, 26, 28, 30-32 and 47-58 under 35 U.S.C. 112, first paragraph have been obviated by the claims amendment filed June 29, 2011.

The rejection of claims 1-2, 5, 12-13, 18, 21, 28, 46-50, 57 and 58 under 35 U.S.C. 103(a) as being unpatentable over WO 97/29114 publication (published August 14, 1997; PTO 1449) in view of WO 99/55367 publication (published November 4, 1999; PTO 1449) or WO 01/00244 (published Jan 2001; PTO 1449) has been obviated by the claims amendment filed June 29, 2011.

Rejection Remain

Claim rejections under - 35 U.S.C. 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 46 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim encompasses numerous conjugate comprising any variants or derivatives of anti-Erb antibody trastuzumab.

The specification discloses just one trastuzumab (HERCEPTIN®) that binds to just human ErbB2. The specification discloses conjugate set forth in claim 27.

The claimed antibody variants and derivatives encompass any substitutions, deletion, addition and combination thereof. There is insufficient description as to where and what amino acids within the full-length antibody trastuzumab that can be altered and still maintains binding specificity to human ErbB2, let alone having an affinity-binding constant of at least $5 \times 10^6 M^{-1}$ when binding to other Erb antigen.

There is no information regarding what structural features, i.e., six CDRs of immunoglobulin heavy and light chain of the encompassed antibodies would likely be associated with which binding specificity, i.e., binding specifically to Erb from human as opposed to other species because the specification does not describe the complete structure, partial structures or physical properties associated with such antibodies. The structure-function correlation set forth in the disclosure does not clearly allow persons of ordinary skill in the art to recognize that the applicant has in fact invented what is claimed because the disclosure only sets forth adequate written description for trastuzumab but not any derivatives and variants thereof with an affinity-binding constant of at least $5 \times 10^6 M^{-1}$. Thus, the functional definition (i.e., at least $5 \times 10^6 M^{-1}$) cannot be correlated with the disclosed structures.

It is known that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (of record, Proc. Natl. Acad. Sci. USA 1982 Vol. 79 page 1979 ; PTO 892). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein

resulted in the loss of antigen-binding function. Furthermore, a method of treating cancer in the absence of *in vivo* working example using any derivative and variants is unpredictable.

For example, Stancovski et al. (of record, Proceedings of the National Academy of Science USA 88: 8691-8695, 1991, PTO 892) characterized the binding effects upon the growth of tumor cells of different antibodies, each of which bind different epitopes of the extracellular domain of a tumor-associated antigen related to EGFR, namely ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually *accelerated* their growth (page 8693, column 1).

Indeed, Riemer et al. (of record, Mol. Immunol. 42: 1121-1124, 2005; PTO 892) teaches, because antibodies binding the same antigens have been shown to both ameliorate and aggravate disease symptoms, the concept of epitope specificity, as opposed to mere antigen specificity, in humoral immunology has gained importance in modern medicine the diverse biological effects; see entire document, particularly page 1123, column 1.

As such, the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well characterized epitope of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish those antibodies that bind an antigen on neoplastic cells and inhibit the growth of those neoplastic cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of neoplastic cells).

Thus, the prior art teaches the therapeutic effectiveness of an antibody that targets cancer cells is not a certainty, and is necessarily determined empirically; and consequently the disclosure cannot be considered to reasonably convey to the skilled artisan Applicant's possession of the claimed invention, since it fails to describe with clarity and particularity the claimed antibody, which can be used as intended. Antibodies that bind to Erb2 are apparently no different.

For example, Cochran et al. (of record, J. Immunol. Meth. 287: 147-158, 2004; PTO 892) describes two anti-EGFR antibodies that bind to spatially overlapping epitopes of EGFR; yet only one of the two competes with EGF for binding to the receptor; see entire document (e.g., page 156, column 1). Thus, an antibody that binds to the same region of EGFR, or perhaps even an antibody that binds to an isoform of EGFR that is expressed in certain cancer cells, but not normal cells, may not have therapeutic value in and of itself, unless it is conjugated to a cytotoxic moiety or capable of mediating antibody dependent cellular cytotoxicity or fixing complement. Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

While method of screening for antibody that binds to Erb2 with high affinity is known in the art, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written

description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences.

Therefore, only the conjugate as set forth in claim 27 comprising trastuzumab as the antibody, trifunctional linking moiety selected from the group consisting of triaminobenzene, tricarboxybenzene, diacarboxyaniline, diamino benzoic acid and biotin or biotin derivative selected from the group consisting of the ones set forth in claim 1, a composition or kit comprising the conjugate of claim 27, but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Applicants' arguments filed June 29, 2011 have been fully considered but are not found persuasive.

Applicants' position is that the claims, as amended, have adequately written description and enabling support. Specifically, the claims have been amended such that the antibody is trastuzumab, the trifunctional linking moiety is triaminobenzene, tricarboxybenzene, diacarboxyaniline, or diamino benzoic acid, and the affinity ligand is biotin, or a biotin derivative selected from the group consisting of norbiotin, homobiotin, oxybiotin, iminobiotin, destibiotin, diaminobiotin, biotin sulfoxide, biotin sulfone, and derivatives thereof having an affinity-binding constant of at least $10^9 M^{-1}$.

In response, claim 46 still recites variants, which encompass any modifications and any derivatives thereof. The claim encompasses any substitutions, deletion, addition and combination thereof. There is insufficient description as to where and what amino acids within the full-length trastuzumab antibody that can be altered and still maintains binding specifically to human ErbB2, let alone having an affinity-binding constant of at least $5 \times 10^6 M^{-1}$ to any Erb antigen.

There is no information regarding what structural features, i.e., six CDRs of immunoglobulin heavy and light chain of the encompassed antibodies variants and derivatives that would likely be

associated with binding specifically to Erb from human as opposed to other species because the specification does not describe the complete structure, partial structures or physical properties associated with such antibodies. Thus the structure-function correlation set forth in the disclosure does not clearly allow persons of ordinary skill in the art to recognize that the applicant has in fact invented what is claimed because the disclosure only sets forth adequate written description for trastuzumab but not any variant or derivative thereof with an affinity-binding constant of at least 5 x 10^6 M^{-1}. Thus, the functional definition (i.e., at least 5 x 10^6 M^{-1}) cannot be correlated with the disclosed structures.

While method of screening for antibody that binds to Erb2 with high affinity is known in the art, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895. For these reasons, the rejection is maintained.

Claim 46 stands are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a conjugate set forth in claims 1, 4-5, 7-10, 18, 21, 26-28, 30-32 and 47-58 **does not** reasonably provide enablement for any conjugates as set forth in claim 46. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Enablement is not commensurate in scope with how to make and use any conjugate comprising any trastuzumab variants and derivatives that encompass any substitutions, deletion, addition and combination thereof.

The specification discloses just one trastuzumab (HERCEPTIN®) that binds to just human ErbB2. The specification discloses conjugate set forth in claim 27.

There is insufficient guidance as to where and what amino acids within the full-length antibody trastuzumab that can be altered and still maintains binding specificity to human ErbB2.

It is known in the art that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (of record, Proc. Natl. Acad. Sci. USA 1982 Vol. 79 page 1979 ; PTO 892). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Furthermore, a method of treating cancer using any conjugate comprising any derivatives or variants in the absence of *in vivo* working example is unpredictable.

For example, Stancovski et al. (of record, Proceedings of the National Academy of Science USA 88: 8691-8695, 1991, PTO 892) characterized the binding effects upon the growth of tumor cells of different antibodies, each of which bind different epitopes of the extracellular domain of a tumor-associated antigen related to EGFR, namely ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually *accelerated* their growth (page 8693, column 1).

Indeed, Riemer et al. (of record, Mol. Immunol. 42: 1121-1124, 2005; PTO 892) teaches, because antibodies binding the same antigens have been shown to both ameliorate and aggravate disease symptoms, the concept of epitope specificity, as opposed to mere antigen specificity, in humoral

immunology has gained importance in modern medicine the diverse biological effects; see entire document, particularly page 1123, column 1.

As such, the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well characterized epitope of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish those antibodies that bind an antigen on neoplastic cells and inhibit the growth of those neoplastic cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of neoplastic cells).

Thus, the prior art teaches the therapeutic effectiveness of an antibody that targets cancer cells is not a certainty, and is necessarily determined empirically. Antibodies that bind to Erb are apparently no different.

For example, Cochran et al. (of record, J. Immunol. Meth. 287: 147-158, 2004; PTO 892) describes two anti-EGFR antibodies that bind to spatially overlapping epitopes of EGFR; yet only one of the two competes with EGF for binding to the receptor; see entire document (e.g., page 156, column 1). Thus, an antibody that binds to the same region of EGFR, or perhaps even an antibody that binds to an isoform of EGFR that is expressed in certain cancer cells, but not normal cells, may not have therapeutic value in and of itself, unless it is conjugated to a cytotoxic moiety or capable of mediating antibody dependent cellular cytotoxicity or fixing complement.

Given the numerous conjugate comprising any trastuzumab variants and derivative thereof, the lack of guidance and insufficient *in vivo* working examples, undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Applicants' arguments filed June 29, 2011 have been fully considered but are not found persuasive.

Applicants' position is that the claims, as amended, have adequately written description and enabling support. Specifically, the claims have been amended such that the antibody is trastuzumab, the trifunctional linking moiety is triaminobenzene, tricarboxybenzene, diacarboxyaniline, or diamino benzoic acid, and the affinity ligand is biotin, or a biotin derivative selected from the group consisting of norbiotin, homobiotin, oxybiotin, iminobiotin, destibiotin, diaminobiotin, biotin sulfoxide, biotin sulfone, and derivatives thereof having an affinity-binding constant of at least $10^9 M^{-1}$.

In response, claim 46 still recites variants, which encompass any modifications and any derivatives thereof. The claim encompasses any substitutions, deletion, addition and combination thereof. There is insufficient guidance and working example as to where and what amino acids within the full-length antibody trastuzumab that can be altered and still maintains binding specifically to human ErbB2 and having an affinity-binding constant of at least $5 \times 10^6 M^{-1}$, let alone binding to any Erb antigen. It is known in the art that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (of record, Proc. Natl. Acad. Sci. USA 1982 Vol. 79 page 1979 ; PTO 892). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Furthermore, the prior art teaches the therapeutic effectiveness of an antibody that targets cancer cells is not a certainty, and is necessarily determined empirically. Antibodies that bind to Erb are apparently no different.

For example, Cochran et al. (of record, J. Immunol. Meth. 287: 147-158, 2004; PTO 892) describes two anti-EGFR antibodies that bind to spatially overlapping epitopes of EGFR; yet only one of the two competes with EGF for binding to the receptor; see entire document (e.g., page 156, column 1). Thus, an antibody that binds to the same region of EGFR, or perhaps even an antibody that binds to an isoform of EGFR that is expressed in certain cancer cells, but not normal cells, may not have therapeutic value in and of itself, unless it is conjugated to a cytotoxic moiety or capable of mediating antibody dependent cellular cytotoxicity or fixing complement.

Given the numerous conjugate comprising any trastuzumab variants and derivative thereof, the lack of guidance and insufficient *in vivo* working examples, undue experimentation would be required to produce the invention commensurate with the scope of the claims. For these reasons, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 5, 7-10, 18, 21, 26, 28, 30-31 and 46-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/02050 publication (of record, published January 13, 2000; PTO 1449) in view of WO 01/00244 (of record, published Jan 2001; PTO 1449) as evidenced by Wilber et al (Bioconjugate Chem 13: 1079-1092, 2002; PTO 1449).

The WO 00/02050 publication teaches a conjugate comprising a) a trifunctional cross-linking moiety such as triaminobenzene, tricarboxybenzene, dicarboxyanline and diaminobenzoic acid (see

Figure at page 1, page 14, line 8-19, claims 1-2, in particular), to which is coupled to b) an affinity ligand such as biotin (see Figure 1, page 9, lines 10-25, in particular) or any biotin derivative thereof such as norbiotin, homobiotin, oxybiotin, iminobiotin, desthiobiotin, diaminobiotin, biotin sulfoxide, biotin sulfone that bind to avidin or streptavidin (see page 11, claims 3-7, in particular) via a linker 1 that contains hydrogen bonding atoms such as ethers, or thioesters, carboxylates, sulfonates, or ammonium group to aid in water solubilization of the biotin in water (see page 15, lines 9-24, claim 9 of the reference, in particular), an effector agent such as radionuclide, Tc-99m, aryl halides, N2S2 N3S chelates for Tc, DTPA, derivatives Me-DTPA, CITC-DTPA, DOTA, TETA, ^{111}In, ^{90}Y, PB, Bi, Cu, Sm, Lu-^{177}, radionuclides (see page 11, lines 19 through page 13, claims 13-15, in particular) or toxin, or drug (see claim 11 of the reference, in particular). The reference linker 1 further comprises a methyl group or alpha carboxylate group in linker 1 (see claim 10 of the reference, in particular) or distance between the bicyclic rings of the biotin moiety as in norbiotin or homobiotin to provide stability toward enzymatic cleavage of the biotinamide bond (see page 15, lines 25-32, claim 7, in particular). The reference linker 1 may be may not be diminished by steric hindrance (see reference claim 8, in particular). The reference linker 2 may be excluded (see claim 16 of the reference, in particular) or a spacer length of 1-25 atoms and contains hydrogen bonding atoms, carboxylates, sulfonates, or ammonium groups (see claims 17-18 of the reference, in particular). The reference effector molecules include toxin, enzyme, immunosuppressive agent, immunostimulating agent, and radionuclide (see claim 29 of the reference, in particular). The publication also teaches a kit comprising the reference conjugate (see claims 28-30 of the reference, in particular). The publication also teaches extracorporeal device for removal of radiolabeled antibody such as avidin coated column (see page 5, line 33-36, in particular). Claim 26 is included in this rejection because it is an obvious variation of the reference teaching since trastuzumab can be linked to either the trifunctional cross-linking moiety or the second linker as taught by the WO 00/02050 publication.

The WO 00/02050 publication does not teach the anti-Erb antibody trastuzumab.

However, the WO 01/00244 publication teaches humanized antibody such as HERCEPTIN® that binds to ErbB2, which is also known in the art as trastuzumab (see entire document, page 43-44, in particular). The reference anti-ErbB2 antibody is conjugated to a toxic agent such as maytansinoid DM-1 (see abstract, example 2, in particular) and composition comprising such for treating cancer expressing ErbB2 (see page 39, claims 1-25 of the reference, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody or scFv antibody in the conjugate of the WO 00/02050 publication for the antibody trastuzumab (HERCEPTIN®) antibody known in the art for treating cancer as taught by the WO01/00244 publication.

One of ordinary skill in the art would have been motivated to and had an expectation of success at the time the invention was made to modify the conjugate of the WO 00/02050 publication in view of the WO 01/00244 publication because humanized anti-ErbB2 antibody such as HERCEPTIN (also known as trastuzumab) is useful delivering cytotoxic agent such as maytansinoid to cancer cell expressing c-erbB2 receptor for treating cancer as taught by the WO 01/00244 publication (see abstract, claims 1-25 of the reference, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to do so because the WO 00/02050 publication teaches biotin compound including modified biotin molecules conjugated with water soluble linker moieties to form biotin dimer, trimer or multimers and one more effectors improves water solubility and resistant to cleavage by serum enzyme biotinidase for use in *in vivo* applications (see page 5, in particular).

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007)* and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and

incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

In this case, simple substitution of the antibody in the biotin trifunctional linking conjugate of the WO 00/02050 publication for the well-known trastuzumab humanized antibody that binds to ErbB2 as taught by WO 01/00244 publication would obtain predictable biotin conjugate.

In this case, applying known technique of making antibody-biotin trifunctional linker conjugate of the WO 00/02050 publication to a known antibody would ready for improving the antibody-biotin conjugate in the same way for treating cancer. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Given the claimed conjugate comprising the same trifunctional reagent diamino benzoic acid containing affinity ligand biotin and cytotoxic agent and anti-Erb antibody trastuzumab are the same as that of the prior art, it is expected that the conjugates have an average of 2 to 4 molecules of said trifunctional crosslinking moiety, biotin affinity and cytotoxic agent as evidentiary reference Wilbur et al (Bioconjugate Chem 13(5): 1079-1092, 2002; PTO 892).

Applicants' arguments filed June 29, 2011 have been fully considered but are not found persuasive.

Applicants' position is that as set forth in the drawing, E means the cytotoxic agent (effector molecule), B means biotin (affinity ligand) and the reagent means the structural features a)-c) in claim 1. In Example 1 of the drawing, the conjugate contains two cytotoxic agents, and in Example 2 of the drawing, the conjugate contains three cytotoxic agents.

Administration of a medical agent containing a cytotoxic agent bound to a tumor surface specific molecule, in this case an anti Erb antibody, i.e. trasuzumab, results in a specific binding of a certain amount of the medical agent to the tumor surface, while the remaining amount of the non-bound medical agent remains for days or weeks in the blood circulation and exposes the body for undesired cytotoxic effects on healthy tissues and organs. Thus, for each kind of cytotoxic agent, a maximum dose to be administered to a subject has been established in the medical community in order to minimize or avoid undesired cytotoxic effects. In addition, prior art cancer therapies administer only one cytotoxic agent per antibody to cancer patients.

However, according to the present invention, more than one, i.e. an average of 2-4, cytotoxic agents per antibody in the conjugate, i.e. the medical agent, may be administrated to a subject. Thus, a higher dose of the cytotoxic agent is effectively targeted close to the tumor surface, to which the antibody part of the conjugate binds and where the cytotoxic agents may exert a therapeutic benefit, e.g. anti-tumor benefit. In other words, the conjugates according to the present invention provide an increased concentration cytotoxic medical agents to tumor cells while decreasing undesired cytotoxicity.

Further, the presence of an average of 2-4 affinity ligands, e.g. biotin, in addition to an average of 2-4 cytotoxic agents in the conjugate facilitates and speeds up the extracorporeal removal of undesired remaining conjugates containing cytotoxic agents circulating in the blood of a subject. Specifically, the adsorption rate of an extracorporeal filter that is used for removing unbound conjugates circulating in the blood of a subject is increased by the increased amount of affinity ligands per conjugate. Thus, the conjugates according to the present invention reduce the time needed for removal of unbound conjugates as compared to the time needed for prior art chemotherapeutics. Consequently, the conjugates of the present invention allow the administration of a higher total dose of a cytotoxic agent to a cancer patient without increasing undesired cytotoxicity as compared to prior art therapeutics.

In addition, the conjugates of the present invention have a unique structure that makes it stable, both on its way to the tumor surface and when present in the blood circulation, which substantially reduces the risk for harmful effects on tissues and organs before the conjugates are extracorporeally

eliminated from the subject's body. Moreover, the unique structure does not negatively influence the binding properties, the biodistribution, and the biokinetics of the anti-Erb antibody.

Nowhere do the cited documents, alone or in combination, teach or suggest binding several molecules, i.e. a)-c) of claim 1, which include both a cytotoxic agent and an affinity ligand, to the one and same antibody in to form a conjugate suitable for use in treatments against cancer or the unexpected advantages of the conjugate - the ability to deliver higher concentrations of medical agents to a tumor without increasing undesired cytotoxicity, easier and faster removal of unbound conjugates circulating in the blood, and improved stability.

With respect to the argument that the drawings Figure 1 and 2 show the conjugate containing an average of 2-4 molecules of a) tri-functional cross-linking moiety, b), an affinity ligand and c) a cytotoxic agent bound to one antibody at the Fc region of the antibody, it is noted that none of the recited claims recite the trifunctional cross-linking moiety, b), an affinity ligand and c) a cytotoxic agent must bound to the Fc region of the antibody as depicted in the drawing in the amendment. Furthermore, given the claimed conjugate comprising the same trifunctional reagent diamino benzoic acid containing affinity ligand biotin and cytotoxic agent and anti-Erb antibody trastuzumab are the same as that of the prior art, it is expected that the conjugates would have an average of 2 to 4 molecules of said trifunctional crosslinking moiety, biotin affinity and cytotoxic agent bound to one antibody as evidentiary reference Wilbur et al (Bioconjugate Chem 13(5): 1079-1092, 2002; PTO 1449).

Evidentiary reference Wilbur et al teach 2 to 3 trifunctional regent diamino benzoic acid containing high affinity ligand biotin and effector moiety per monoclonal antibody (see page 1086, Table 1, columns 2 and 3, in particular). It is within the purview of one of ordinary skill in the chemical conjugate art to increase the number of effector molecules per antibody for radiation therapy. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Claims 1, 4-5, 7-10, 18, 21, 26-28, 30-31 and 46-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/02051 publication (of record, published January 2000; PTO 892) in view of WO 01/00244 publication (of record, published January 2000; PTO 892) as evidenced by Wilbur et al (bioconjugate Chem 13: 1079-1092, 2002; PTO 1449).

WO 00/02051 publication discloses a conjugate comprising components a)-d) of claim 1 (see entire document, page 1, claims 1-24, page 6, in particular). The WO 00/02051 publication discloses use of affinity ligand such as biotin or biotin derivative such as norbiotin, homobiotin, oxybiotin, iminobiotin, desthiobiotin, diaminobiotin, biotin sulfoxide, biotin sulfone and cytotoxic agent such as DOTA in said conjugate (see claims 5, 14, page 12, in particular). The biomolecule use in the conjugate can be an antibody which binds tumors (see pages 6-7) wherein the conjugate also uses a radiolabeled effector (see page 6). The conjugate uses the same components recited in the claimed invention and would therefore bind the same number of antibody molecule. The WO 00/02051 publication teaches trifunctional cross-linking moiety such as triaminobenzene, tricarboxybenzene, diacarboxyaniline, and diaminobenzoic acid (see page 16, claim 5, in particular). The reference trifunctional cross-linking moiety includes triaminobenzene, tricarboxybenzene, diacarboxyaniline or diaminobenzoic acid (see Figure at page 1, page 16, claims 2, in particular), to which is coupled to b) an affinity ligand such as biotin (see Figure 1, page 12, in particular) or biotin derivative thereof such as norbiotin, homobiotin, oxybiotin, iminobiotin, desthiobiotin, diaminobiotin, biotin sulfoxide, biotin sulfone that bind to avidin or streptavidin (see page 12, lines 21-25, claims 5-6, in particular) via a linker 1 that contains hydrogen bonding atoms such as ethers, or thioether, carboxylates, sulfonates, or ammonium group to aid in water solubilization of the biotin in water (see pages 16-17, claims 8-10 of the reference, in particular). The reference effector agent is a radionuclide such as Tc-99m, aryl halides, N2S2 N3S chelates for Tc, DTPA, derivatives Me-DTPA, CITC-DTPA, DOTA, TETA, ^{111}In, ^{90}Y, PB, Bi, Cu, Sm, Lu-^{177} (see page 11, claims 11-15, in particular) or toxin, or drug (see page 11, claim 11 of the reference, in particular). The reference linker 1 further

comprises a methyl group or alpha carboxylate group in linker 1 (see claim 9 of the reference, in particular) or distance between the bicyclic rings of the biotin moiety as in norbiotin or homobiotin to provide stability toward enzymatic cleavage of the biotinamide bond (see claim 7, in particular). The reference linker 1 may be may not be diminished by steric hindrance (see reference claim 8, in particular). The reference linker 2 may be excluded (see page 12, lines 1-5, claim 17 of the reference, in particular) or a spacer length of 1-25 atoms and contains hydrogen bonding atoms, carboxylates, sulfonates, or ammonium groups (see claims 18-19 of the reference, in particular). The reference linker 3 may be excluded (see page 12, lines 1-5, claim 21 of the reference, in particular) or a spacer length of 1-25 atoms and contains hydrogen bonding atoms, carboxylates, sulfonates, or ammonium groups (see claims 22-23 of the reference, in particular). The reference effector molecules include toxin, enzyme, immunosuppressive agent, immunostimulating agent or radionuclide (see claims 11 and 31 of the reference, in particular). The publication also teaches a kit comprising the reference conjugate (see claims 30-32 of the reference, in particular). The publication also teaches extracorporeal device for removal of radiolabeled antibody such as avidin coated column (see claims 29-30, in particular). The reference conjugate is administered intravenously (see page 6, line 26, in particular). Claim 26 is included in this rejection because it is an obvious variation of the reference teaching since trastuzumab can be linked to either the trifunctional cross-linking moiety or the second linker as taught by the WO 00/02051.

The WO 00/02051 publication does not teach the anti-Erb2 antibody which is trastuzumab.

However, the WO 01/00244 publication teaches humanized antibody such as HERCEPTIN® that binds to ErbB2, which is also known in the art as trastuzumab (see entire document, page 43-44, in particular). The reference anti-ErbB2 antibody is conjugated to a toxic agent such as maytansinoid DM-1 (see abstract, example 2, in particular) and composition comprising such for treating cancer expressing ErbB2 (see page 39, claims 1-25 of the reference, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody or scFv antibody in the conjugate of the WO 00/02051 publication for the antibody trastuzumab (HERCEPTIN®) antibody linked to toxin known in the art for treating cancer as taught by the WO01/00244 publication.

One of ordinary skill in the art would have been motivated to and had an expectation of success at the time the invention was made to modify the conjugate of the WO 00/02051 publication in view of the WO 01/00244 publication because humanized anti-ErbB2 antibody such as HERCEPTIN (also known as trastuzumab) is useful delivering cytotoxic agent such as maytansinoid to cancer cell expressing c-erbB2 receptor for treating cancer as taught by the WO 01/00244 publication (see abstract, claims 1-25 of the reference, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to do so because the WO 00/02051 publication teaches biotin compound including modified biotin molecules conjugated with water soluble linker moieties to form biotin dimer, trimer or multimers and one more effectors improves water solubility and resistant to cleavage by serum enzyme biotinidase for use in *in vivo* applications (see page 6, 17, in particular).

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007)* and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

In this case, applying known technique of making antibody-biotin trifunctional linker conjugate of the WO 00/02051 publication to an antibody would ready for improving the antibody-biotin conjugate in the same way. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Given the claimed conjugate comprising the same trifunctional reagent diamino benzoic acid containing affinity ligand biotin and cytotoxic agent and anti-Erb antibody trastuzumab are the same as that of the prior art, it is expected that the conjugates have an average of 2 to 4 molecules of said trifunctional crosslinking moiety, biotin affinity and cytotoxic agent as evidentiary reference Wilbur et al (Bioconjugate Chem 13(5): 1079-1092, 2002; PTO 892). Evidentiary reference Wilbur et al teach 2 to 3 trifunctional regent diamino benzoic acid containing high affinity ligand biotin and effector moiety per monoclonal antibody (see page 1086, Table 1, columns 2 and 3, in particular). It is within the purview of one of ordinary skill in the chemical conjugate art to increase the number of effector molecules per antibody for radiation therapy. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

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Further, the presence of an average of 2-4 affinity ligands, e.g. biotin, in addition to an average of 2-4 cytotoxic agents in the conjugate facilitates and speeds up the extracorporeal removal of undesired remaining conjugates containing cytotoxic agents circulating in the blood of a subject. Specifically, the adsorption rate of an extracorporeal filter that is used for removing unbound conjugates circulating in the blood of a subject is increased by the increased amount of affinity ligands per conjugate. Thus, the conjugates according to the present invention reduce the time needed for removal of unbound conjugates as compared to the time needed for prior art chemotherapeutics. Consequently, the conjugates of the present invention allow the administration of a higher total dose of a cytotoxic agent to a cancer patient without increasing undesired cytotoxicity as compared to prior art therapeutics.

In addition, the conjugates of the present invention have a unique structure that makes it stable, both on its way to the tumor surface and when present in the blood circulation, which substantially reduces the risk for harmful effects on tissues and organs before the conjugates are extracorporeally eliminated from the subject's body. Moreover, the unique structure does not negatively influence the binding properties, the biodistribution, and the biokinetics of the anti-Erb antibody.

Nowhere do the cited documents, alone or in combination, teach or suggest binding several molecules, i.e. a)-c) of claim 1, which include both a cytotoxic agent and an affinity ligand, to the one and same antibody in to form a conjugate suitable for use in treatments against cancer or the unexpected advantages of the conjugate - the ability to deliver higher concentrations of medical agents to a tumor without increasing undesired cytotoxicity, easier and faster removal of unbound conjugates circulating in the blood, and improved stability.

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The following new ground of rejection is necessitated by the amendment filed June 29, 2011.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 46 recites the limitation "anti-Erb antibody *variants are any modifications, fragments or derivatives*" in claim 46. There is insufficient antecedent basis for this limitation in the claim. This is because the term "variants thereof" in claim 1 has been deleted.

Claim 32 recites the limitation "the affinity ligand is *absent*...the *immobilized receptor*" in claim 32. There is insufficient antecedent basis for this limitation in the claim because the affinity ligand is present in conjugate of claims 30, 28 and 1 to which claim 32 depends from.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644